MEMORANDUM

Date: January 21, 2011

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application RT2-01939

Enclosed is a petition letter from Dr. Stefan Heller of Stanford University, an applicant for funding under RFA 10-02, CIRM Tools and Technology II Awards. This letter was received at CIRM on January 19, 2011 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

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Extraordinary Petition for ICOC Consideration of Application RT2-01939 for Funding

To the Chairman of the ICOC (Robert Klein, J.D.), the President of CIRM (Alan Trounson, Ph.D.), and the Chief Scientific Officer of CIRM (Gilberto Sambrano, Ph.D.)

January 18, 2011

Dear Drs. Klein, Trounson, and Sambrano:

Our joined application *RT2-01939 Hearing loss in-a-dish model for otoprotective and otoregenerative drug development* has been reviewed by a German BMBF review panel and the CIRM scientific review committee. It has been recommended for funding by the BMBF, and it has received from the CIRM review committee a final score of 72.

During the programmatic review, the motion was made to move our application into Tier 1 on grounds of programmatic need, particularly because it is an important project in a specialized area of translational research that is not well represented in CIRM's grant portfolio but affecting a large number of patients. The motion failed.

We would like you to consider the following arguments before reaching a final decision about our application:

1) The medical need. As researchers in a small and specialized field, we noticed that the review report clearly shows that reviewers had split views about the feasibility of our approach, previous productivity, as well as about the programmatic "need" to sponsor research in our field. We believe that the reviewers were not appropriately calibrated with respect to the state of the science in our field, which consists of only a few laboratories – compared to larger fields with many well-funded laboratories. On the other hand, successful development of novel therapies for hearing loss and balance disorders would affect the lives of millions of patients. Therefore, research activity in our field clearly remains disproportionate to the major medical need.

2) Purpose and Objectives of the RFA. We acknowledge that our research progress faces a major bottleneck that is to generate enough pure human inner ear progenitor cells for drug screens. The whole point of the RFA was to identify translational bottlenecks and to come up with strategies to overcome these existing bottlenecks. Bottlenecks imply difficulties and risks. In our application, we explained the bottleneck - that is - not being able to generate enough cells for drug screening assays, and we described that, once the bottleneck is removed, we will be able to develop novel assays for treatment. The main critique, however, that prevailed was that all the planned assay development is not feasible because we were unable to generate enough human otic progenitors. A clear Catch 22, and a very disarming argument, which clearly did not

take into account the purpose and objectives for the Tools and Technology RFA (*removal of existing translational bottlenecks*).

3) Regarding productivity. During the review process, a motion was made to move our application to Tier 1 on grounds of programmatic need. The motion was not successful, and we noticed that the disarming, but vague argument of feasibility, which appeared to be interpreted as a lack of productivity (in the sense of "little progress was reported despite an ongoing CIRM-funded effort"). The Heller lab is CIRM funded for 3 1/2 years and we have had several publications arising from CIRM funding including a major recent one in the journal *Cell* on mouse ESC guidance. The main results of our human ESC study are unpublished, we agree with this critique, but this does not mean that we have not made progress. We currently are at a point where we have developed a highly reliable protocol to generate human otic progenitors that differentiate well into human inner ear cell types. This work will be presented for the first time at the Stanford Stem Cell Institute's annual retreat on January 24/25. Our ongoing CIRM comprehensive research grant has been funded based on a specific time plan and our current progress is very much in line with the original time plan.

4) Regarding feasibility of the approach. Our hESC guidance protocol is clearly at a point where we are able to generate human inner ear sensory hair cells as well as their surrounding supporting cells in a culture dish. These cells are identified by co-expression of several identifying markers as well as by existence of F-actin filled protrusions that are immuno-positive for identifying hair bundle proteins. This data was not shown in the application because the application dealt with finding ways to enrich for otic progenitor cells (and not mature cells). Furthermore, a recent breakthrough directly addresses the feasibility critique: we completely eliminated the need for using unspecified extracellular matrix (co-culturing with other cells), which substantially increases our ability to generate inner ear cell types. Our current protocol is able to generate human inner ear cell types reliably and without using any animal products. Some of this progress happened recently, and other experiments were not presented in the grant application because we believed that our published work on mouse ESCs would show our capability to handle such a project. In fact, the review noted, that "based on the experience and track record, reviewers were convinced of the PI's capacity to oversee a project of this scope".

5) Why no publications on human ESCs (yet)? Our group has set the standard for in-depth characterization of ESC-generated sensory hair cells, which includes showing complex cytomorphology by electron microscopy and electrophysiological demonstration of functional mechanosensation. Proper electrophysiological assessment requires time and care. We will not publish our human results unless we can meet our own scientific standards set forth in previous publications in high-impact journals. We believe that such standards are extremely important particularly for being a representative laboratory of a small field. If showing of immuno-positive cells in a dish would be the goal, we would have already submitted a manuscript, which probably would have been evidence enough for convincing the reviewers of this application of feasibility of our approach. Nevertheless, our goal is to show functional data, which in our case consists of complex electrophysiological assessment whether the inner ear sensory cell type that we generate is indeed a <u>functional</u> cell. We are one of less than five laboratories working on stem cell related approaches to find treatments for hearing loss. We strongly believe that our science has to be exemplary as one of the few representative laboratories of the field.

6) Our research group is an asset for CIRM in a small and specialized field with a high medical need. We have established a working and productive CIRM-funded group of people that joined us from outside the inner ear field that now, after 3 years, has reached a level of competence and productivity that comes close to groups working in much larger fields with more depth in basic science, as well as a much larger pool of personnel that readily joins these laboratories. Without the investment from CIRM, this group would not exist! Now is the time to build on this asset and not to stop the funding and to disperse the researchers. There are few laboratories in our field and progress is carried by a much smaller group of people than some of the larger fields that are well-supported by CIRM. Yet, a larger field much easier absorbs a major individual funding gap, whereas lack of sufficient funds will most certainly substantially hamper any progress in the hearing loss treatment field because we will lose the best and brightest co-workers of our laboratory. Our inner ear hESC group at Stanford would be in danger of dissolving, and research on the topic would have to start all over again, possibly severely slowing down the translation of hESC technology into the hearing loss field, thereby affecting millions of patients.

7) German BMBF - CIRM collaboration. We have reached out to a strong German collaborator, which was considered by the reviewers as complementary with clear evidence of a well-conceived, ongoing collaboration. For our field, such an international collaboration is unprecedented - a collaboration of two out of the five leading laboratories will clearly expedite the discovery of novel treatments for patients. Finally, we also would like to note that our joined application was recommended for funding by the BMBF review panel in Germany. Investment by CIRM in this research would leverage funds from the BMBF, thereby further fostering research in the small and specialized field of hearing loss treatment. Also, both laboratories would benefit from the planned exchange of highly qualified post-doctoral researchers.

8) Job creation. This *Tools and Technology* grant application directly deals with removing the only existing bottleneck preventing the development of the first high-throughput drug discovery screens in the hearing space. We have been extensively talking with potential investors as well as with multiple big pharmaceutical corporations about feasibility of our approach particularly with respect of using the assay as asset for a new biotech firm. We have been meeting with high-throughput screening experts from two out of the top ten big pharmaceutical companies and have discussed our planned hESC-based screening assays with them. Removal of the existing bottleneck, the main topic of our grant application, will directly expedite the founding of a new drug-discovery company in the hearing field locally in the SF Bay area. Not having the funding available, on the other hand, will most certainly hamper, slow down, or even de-rail our plans for translating our research into a new local biotech firm.

We hope that these arguments will lead to a re-consideration of our application. For any questions, please feel free to contact us either by phone or by e-mail.

Sincerely yours,

Stefan Heller, PhD – Stanford University; Hubert Löwenheim, MD – University of Tübingen